PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07H 17/08 — A1

(11) International Publication Number: **WO 00/14099**

(43) International Publication Date: 16 March 2000 (16.03.00)

(21) International Application Number: PCT/KR99/00530

(22) International Filing Date: 8 September 1999 (08.09.99)

(30) Priority Data:
1998/37181 9 September 1998 (09.09.98) KR

(71) Applicant *(for all designated States except US)*: HANMI PHARM. CO., LTD. [KR/KR]; #893–5, Hajeori, Paltan-myeon, Hwaseonggun, Kyungki–do 445–910 (KR).

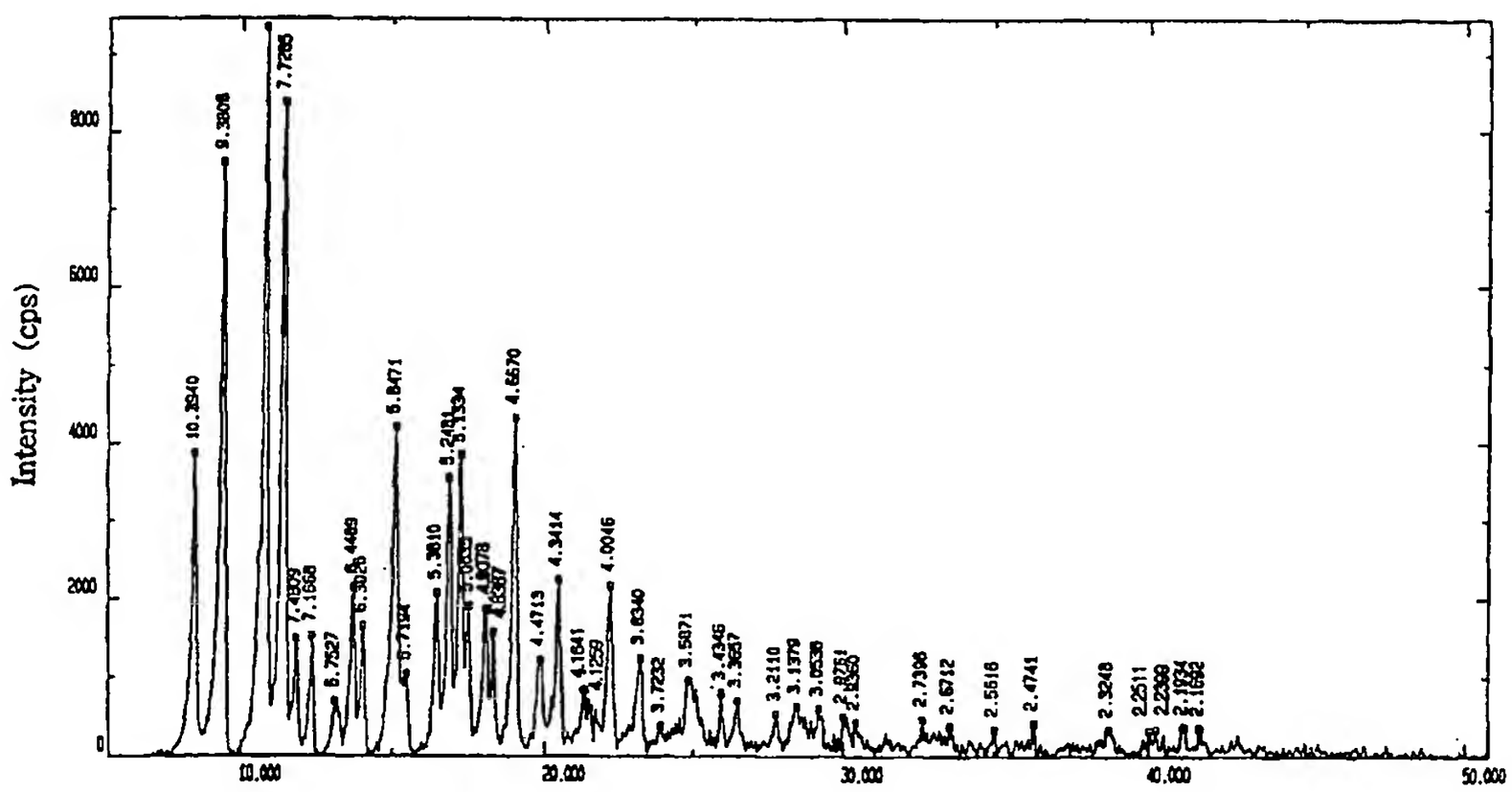
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LEE, Tae, Suk [KR/KR]; Hanyang Apt., 603–709, Yangjimaeul, #29, Sunae–dong, Bundang–gu, Seongnam–shi, Kyungki–do 463–020 (KR). LEE, Ju, Cheol [KR/KR]; #633–7, Gui–1–dong, Kwangjin–gu, Seoul 143–201 (KR). LEE, Kyoung, Ik [KR/KR]; #542–1, Ganseok–1–dong, Namdong–gu, Incheon 405–231 (KR). LEE, Gwan, Sun [KR/KR]; Geuk-dong Apt., 2–806, Garak–dong, Songpa–gu, Seoul 138–160 (KR). KIM, Wan, Joo [KR/KR]; Olympicseonsuchon Apt., 311–1002, #89, Bangi–dong, Songpa–gu, Seoul 138–050 (KR).

(74) Agents: JANG, Seong, Ku et al.; 17th floor, KEC Building, #275–7, Yangjae–dong, Seocho–ku, Seoul 137–130 (KR).

(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD OF PREPARING FORM II CRYSTALS OF CLARITHROMYCIN



(57) Abstract

Form II crystals of clarithromycin can be easily prepared by treating clarithromycin of different crystal forms with water or with a mixture of water and a water–immiscible organic solvent and isolating treated crystals by filtration.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

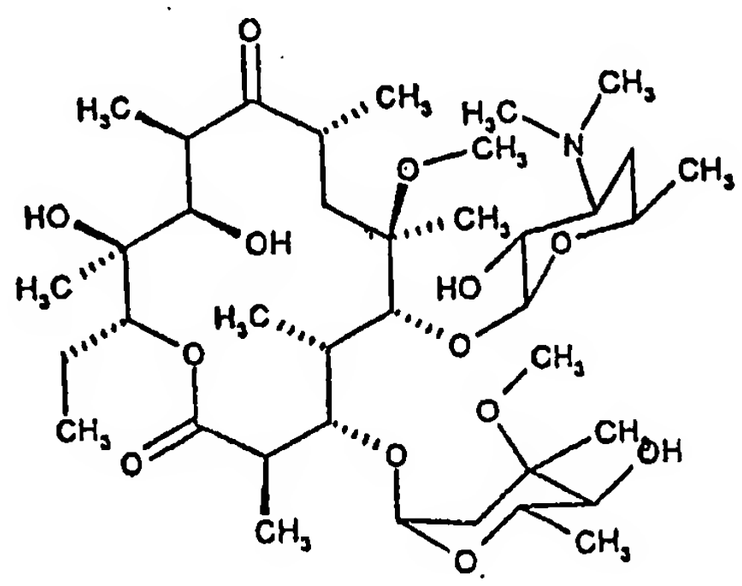
METHOD OF PREPARING FORM II CRYSTALS OF CLARITHROMYCIN

FIELD OF THE INVENTION

The present invention relates to a method of preparing Form II crystals of clarithromycin comprising treating clarithromycin with water to provide said crystals having no residual organic solvent.

BACKGROUND OF THE INVENTION

Clarithromycin, 6-O-methylerythromycin A, is a semisynthetic macrolide antibiotic of formula (I) which exhibits a wide range of antibacterial activity:



(I)

It has been discovered that clarithromycin exists in two distinct crystalline forms, "Form I" and "Form II", as described in International Publication Nos. WO 98/04573 and WO 98/04574. The crystal forms can be identified by infrared spectroscopy, differential scanning calorimetry and powder x-ray diffraction spectrophotometry. Form I crystals of clarithromycin are prepared by recrystallization from ethanol, tetrahydrofuran, isopropyl acetate, isopropyl alcohol or a mixture thereof. However, the thermodynamically more stable Form II is used in the drug formulations currently on the market.

Form II crystals of clarithromycin have been prepared by crystallization from chloroform/isopropyl ether (1:2) (see Merck Index 12th ed., pp. 395), but this method has a

problem in that the resulting Form II crystals contain residual organic solvents. Alternatively, Form II crystals may be obtained by heating Form I crystals under a vacuum at 80°C or higher for a prolonged time (see International Publication No. WO 98/04573), but this method has the problem of low productivity.

International Publication No. WO 98/04574 teaches a method of preparing clarithromycin crystal Form II using various organic solvent systems or aqueous solvents containing water-miscible organic solvents. However, this method is hampered by a relatively low yield (approximately 9 to 83%) and still has the problem of entrained organic solvents.

Accordingly, there has existed a need to develop a new simple method for preparing pure Form II crystals of clarithromycin in a high yield.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the present invention to provide pure Form II crystals of clarithromycin having no residual solvent in a high yield.

In accordance with the present invention, there is provided a method of preparing Form II crystals of clarithromycin comprising treating clarithromycin with water or with a mixture of water and a water-immiscible organic solvent.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description, when taken in conjunction with the accompanying drawing wherein:

Fig. 1 shows the powder X-ray diffraction spectrum of clarithromycin crystal Form II.

DETAILED DESCRIPTION OF THE INVENTION

The method of preparing Form II crystals of clarithromycin in accordance with the present invention comprises the step of treating clarithromycin with water or with a mixture of water and a water-immiscible organic solvent and isolating treated crystals.

The term "clarithromycin" as used herein refers to refined crystal Form I or mixtures of refined crystal Form I and Form II, or crude reaction product formed during the process of the preparation thereof. Representative methods of preparing clarithromycin are described in U.S. Patent Nos. 4,331,803, 4,670,549, 4,672,109 and 4,990,602, and European Patent No. 260 938.

The treating step in accordance with the present invention may be performed at an ambient temperature with stirring for a period sufficient to convert Form I crystals to Form II crystals of clarithromycin, e.g., about 1 to 4 hours.

Water which may be distilled or deionized water is used in the inventive process in an amount ranging from 3 to 10 times that of clarithromycin used.

The water-immiscible organic solvents optionally used in the present invention are those which do not dissolve clarithromycin to any significant extent, and examples thereof include C_{5-7} hydrocarbons, diethyl ether, ethyl acetate, methyl acetate and the like. The optional water-immiscible organic solvent functions to dissolve impurities that may be present in a clarithromycin feed, thereby further increasing the purity of the product. The organic solvent may be employed in an amount ranging from 0.5 to 2 times that of clarithromycin used.

After the clarithromycin crystals are sufficiently treated, the resultant crystals are filtered and dried in a conventional manner to give pure clarithromycin crystal Form II in a high yield of at least 95%.

The method of the present invention is very simple and

provides pure Form II crystals of clarithromycin having no residual organic solvent in a high yield of greater than 95% at a low process cost.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Example 1 : Recovering of Form II crystals of clarithromycin from Water

100g of clarithromycin (purity: 95.5%) was added to 500ml of water and the resulting mixture was stirred vigorously at room temperature for 2 hours. The crystals were filtered and dried overnight in a vacuum oven of 60°C to give 97g of clarithromycin crystal Form II (purity: 97.4%, yield: 97%).

Example 2 : Recovering of Form II crystals of clarithromycin from Water and Hexane

100g of clarithromycin (purity: 95.5%) was added to 500ml of water and the resulting mixture was stirred vigorously at room temperature for 2 hours. 100ml of hexane was added thereto, and the mixture was further stirred at room temperature for 1 hour. The resulting crystals were filtered and dried overnight in a vacuum oven of 60°C to give 95g of clarithromycin crystal Form II (purity: 97.7%, yield: 95%).

Example 3 : Recovering of Form II crystals of clarithromycin from Water and Ethyl acetate

The procedure of Example 2 was repeated except that ethyl acetate was used instead of hexane, to give 95g of clarithromycin crystal Form II (purity: 98.0%, yield: 95%).

Example 4 : Recovering of Form II crystals of clarithromycin from Water and Methyl acetate

The procedure of Example 2 was repeated except that methyl acetate was used instead of hexane, to give 95g of clarithromycin crystal Form II (purity: 97.9%, yield: 95%).

Example 5 : Recovering of Form II crystals of clarithromycin from Water and Diethyl Ether

The procedure of Example 2 was repeated except that diethyl ether was used instead of hexane, to give 97g of clarithromycin crystal Form II (purity: 97.5%, yield: 97%).

The powder X-ray diffraction pattern of each clarithromycin obtained in Examples 1 to 5 was identical to that of clarithromycin crystal Form II shown in Figure 1.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

What is claimed is:

1. A method of preparing Form II crystals of clarithromycin comprising treating a clarithromycin feed with water or with a mixture of water and a water-immiscible organic solvent and isolating treated crystals by filtration.

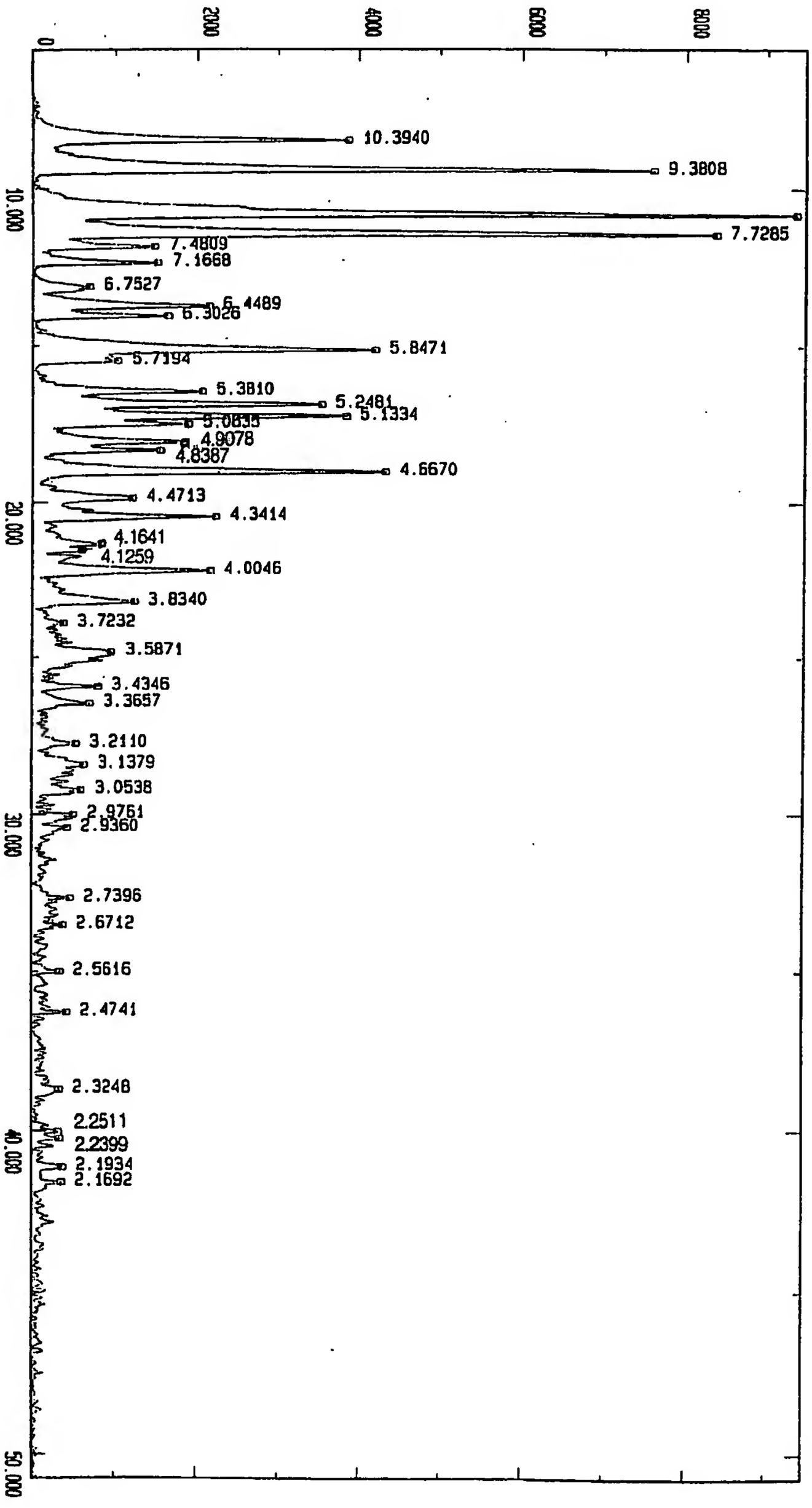
2. The method of claim 1, wherein the water-immiscible organic solvent is selected from the group consisting of a C_{5-7} hydrocarbon, diethyl ether, ethyl acetate and methyl acetate.

3. The method of claim 1 or 2, wherein the water-immiscible organic solvent is hexane.

4. The method of claim 1, wherein water is used in an amount ranging from 3 to 10 times that of the clarithromycin feed.

5. The method of claim 1, wherein the water-immiscible organic solvent is used in an amount ranging from 0.5 to 2 times that of the clarithromycin feed.

Fig. 1


Intensity (cps)
0
2000
4000
6000
8000
2Theta (deg.)
10.000
20.000
30.000
40.000
50.000
10.3940
9.3808
7.7285
7.4809
7.1668
6.7527
6.4489
6.3026
5.8471
5.7194
5.3810
5.2481
5.1334
5.0635
4.9078
4.8387
4.6670
4.4713
4.3414
4.1641
4.1259
4.0046
3.8340
3.7232
3.5871
3.4346
3.3657
3.2110
3.1379
3.0538
2.9761
2.9360
2.7396
2.6712
2.5616
2.4741
2.3248
2.2511
2.2399
2.1934
2.1692

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00530

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07H 17/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07H, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/04574 A1 (ABBOTT LABORATORIES) 05 February 1998 (05.02.98), claims. (Cited in the application).	1-5
A	WO 98/04573 A1 (ABOTT LABORATORIES) 05 February 1998 (05.02.98), claims. (Cited in the applications).	1-5
A	WO 98/31699 A1 (ABBOTT LABORATORIES) 23 July 1998 (23.07.98), claims.	1-5

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed

„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1999 (25.11.99)	21 January 2000 (21.01.00)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Authorized officer Schnass Telephone No. 1/53424/217

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 99/00530

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	A1	9804574	05-02-1998	AU	A1	37405/97	20-02-1998
				EP	A1	915899	19-05-1999
				US	A	5844105	01-12-1998
WO	A1	9804573	05-02-1998	AU	A1	37397/97	20-02-1998
				CA	AA	2258606	05-02-1998
				CN	A	1229411	22-09-1999
				CZ	A3	9900099	12-05-1999
				EP	A1	915898	19-05-1999
				US	A	5858986	12-01-1999
WO	A1	9831699	23-07-1998	AU	A1	55326/98	07-08-1998
				US	A	5945405	31-08-1999
				ZA	A	9800116	08-07-1998